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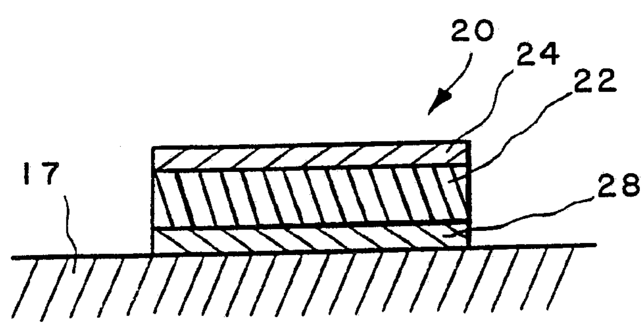

(57) Abstract

The present invention provides compositions and methods for the transdermal administration of a contraceptively effective amount of gestodene and an estrogen, such as ethinyl estradiol, in combination, together with a suitable permeation enhancer.

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TRANSDERMAL CONTRACEPTIVE FORMULATIONS, METHODS AND DEVICES

RELATED APPLICATIONS

This is a continuation-in-part of U.S. application Serial No. 07/605,581, filed October 29, 1990, which application is incorporated herein by reference and benefit is claimed of its filing date.

FIELD OF THE INVENTION

This invention relates to transdermal drug delivery. More particularly, this invention relates to contraceptive delivery and, still more particularly but without limitation thereto, this invention relates to the transdermal delivery, in combination, of gestodene and estrogens, such as ethinyl estradiol, at contraceptively effective rates.

BACKGROUND OF THE INVENTION

The transdermal route of parenteral delivery of drugs provides many advantages, and transdermal systems for delivering a wide variety of drugs or other beneficial agents are described in U.S. Pat. Nos. 3,598,122, 3,598,123, 4,379,454, 4,286,592, 4,314,557 and 4,568,343, for example, all of which are incorporated herein by reference.

Gestodene is a known orally active synthetic progestogen with a progesterone-like profile of activity (see, U.S. Pat. 4,081,537). It is used as an oral contraceptive in combination with certain estrogens.

Oral combination pills and intrauterine devices for purposes of contraception have been well documented for their problems such as inconvenience and side effects. Transdermal delivery of contraceptives as disclosed herein is an attempt to eliminate or reduce those problems.

However, there are many factors which affect the suitability of an active agent for transdermal administration. These are discussed at length in Knepp et al., "Transdermal Drug Delivery: Problems and Possibilities," <u>CRC Critical Reviews in Therapeutic Drug Carrier</u>

Systems, Vol. 4, Issue 1 (1987). When it is desired to deliver more than one active agent from a single transdermal delivery device, the problems associated with achieving a workable multi-drug transdermal device with any specific combination of drugs are even more complex and difficult and can often prove to be insurmountable.

Conventional dosage forms such as tablets or injections can administer a combination of two or more active agents, each at their appropriate dose, merely by appropriate selection of the amount of each agent included in the dosage form. In transdermal delivery devices, however, the total dosage of each agent is not established by the amounts of each agent that are in the device. Instead, the total dosage of each agent is the product of its average transdermal administration rate (μg/hr) and the time over which the device is applied, and the average administration rate of an agent from a transdermal delivery device is determined primarily by a combination of factors other than the amount of the agent present in the device.

In order for a transdermal delivery device to be able to administer two or more agents from a common reservoir over the same period of time, the relative permeabilities of each of the agents through the skin and the components of the device must bear the same relationship as their relative dosage or administration rate. Thus, for example, if the dosage of each agent were the same, for example 15 μg/day, each agent would have to have the same overall permeability. If, however, one agent were to be delivered at a dosage of 20 μg/day and the other at 1 μg/day, the overall permeability of one would have to be 20 times greater than that of the other.

The situation becomes even more complicated if permeation enhancers are required to increase the inherent permeability of the skin to one or more of the agents being delivered. Identifying a permeation enhancer which has the ability to selectively increase the permeation of the skin to only one agent or to relatively increase the permeability of the skin to two or more agents in the required relationship could often provide an insurmountable obstacle for any specific combination of agents.

If the problems associated with obtaining the desired relative administration rates of the individual agents to the skin can be solved, other factors remain to be dealt with. The agents individually, in combination with each other, or in combination with a permeation enhancer must not cause undue irritation or sensitization when applied topically under occlusion. Materials which individually are not irritating or sensitizing may become so when presented to the skin in combination with each other.

Further, the skin has been recognized as the largest metabolizing organ of the body, larger even than the liver. See, A. Pannatier, et al, "The Skin as a Drug Metabolizing Organ," Drug Metabolism Reviews, Vol. 8, No. 2, pp 319-43 (1978). Skin can metabolize agents administered transdermally into inactive or potentially harmful metabolites. Thus, it is necessary that the rate at which each agent is metabolized by the skin and the metabolites produced do not prevent the safe and therapeutically effective transdermal administration of each agent into the bloodstream at the desired administration rate.

Assuming these obstacles can be overcome, it is also important that the agent binding capacity of the skin for each of the agents have the proper relationship. Before transdermal administration of an agent into the bloodstream can commence at a steady state rate, the capacity of the skin below the device to bind the agent must be saturated. The time required to achieve this steady state rate is known as the "lag time" and is a function of the rate at which the agent permeates into the skin and the binding capacity of the skin for that agent. In order for the lag time for both agents to be the same, there must be an inverse relationship between each agent's administration rate and the binding capacity of the skin for each agent.

Thus, while there are numerous combinations of beneficial agents which have been found useful for administration orally or by injection, for example, it is by no means obvious that a particular combination of such agents or other agents could also be safely and effectively administered transdermally.

U.S. Pat. 4,816,258 discloses a transdermal delivery system for administering ethinyl estradiol and levonorgestrel, together with a permeation enhancer, as a contraceptive.

However, it has now been found by the present inventors that levonorgestrel, even in the presence of a permeation enhancer such as glycerol monooleate, does not transport across human epidermis in vivo sufficiently to achieve therapeutically (i.e., contraceptively) effective levels of the drug in the blood from transdermal systems of reasonable or acceptable size.

Surprisingly, it has now been seen that gestodene, while being approximately equipotent with levonorgestrel when applied orally, acts very differently from levonorgestrel when applied transdermally. Gestodene, unpredictably, has a greatly increased flux in comparison to levonorgestrel, which flux is sufficient when applied transdermally to provide blood drug levels from reasonably sized systems in amounts that produce effective contraception, in marked contrast to levonorgestrel.

Australian patent AU-A-15323/88 discloses a transdermal delivery system for the delivery of estrogens and synthetic gestogens for the treatment of climacteric syndrome (the withdrawal symptoms associated with menopause and caused by estrogen deficiency). The patent makes a general statement that natural gestogens, such as progesterone, do not pass through the skin in amounts sufficient to achieve adequate therapeutic effect using transdermal systems of conventional size but that synthetic gestogens do have sufficient flux. Levonorgestrel (or d-norgestrel) is named in the patent as a synthetic gestogen which can be used in the transdermal system, and norgestrel and norethisterone-17-acetate are named as preferred synthetic gestogens for use in the system. Gestodene is not mentioned as a candidate gestogen. It is to be noted here that a markedly greater amount of a gestogen and, consequently, a greater transdermal flux of the drug, is required for effective contraception than is required for treatment of climacteric syndrome. As discussed previously herein, it has been shown that levonorgestrel, the active enantiomer of the preferred gestogen norgestrel, does not, in fact, have a sufficient flux to provide a contraceptively effective amount

of drug in vivo when applied transdermally from a reasonably sized system. Additionally, norethisterone-17-acetate (also known as norethindrone-17-acetate and the only drug for which actual data is presented in the Australian patent) has also been found to have an insufficient transdermal flux from a reasonably sized system to provide sufficient blood levels for effective contraception. These facts show that the broad statement in the Australian patent is not in fact generally true and that sufficient flux of synthetic gestogens, particularly with respect to providing a contraceptive effect, is a continuing problem and cannot be predicted.

Thus, it is by no means obvious that a particular synthetic gestogen could be effectively administered transdermally, with or without an estrogen, and especially in an amount sufficient to provide a contraceptive effect. That the gestogen could be delivered in a contraceptively effective amount from a reasonably sized system is especially desired and even less predictable or obvious.

U.S. Pat. No. 4,286,592 discloses a transdermal system with a contact adhesive layer, where the adhesive layer controls the rate at which drug is released to the skin.

U.S. Pat. No. 4,379,454 discloses a transdermal system which includes a rate controlling layer for controlling the rate at which an absorption enhancer is released to the skin.

U.S. Pat. No. 4,863,738 discloses glycerol monooleate as a suitable skin permeation enhancer for steroids.

U.S. Pat. No. 4,746,515 discloses glycerol monolaurate as a suitable skin permeation enhancer for steroids.

SUMMARY OF THE INVENTION

An object of the present invention is to provide delivery of contraceptives by means of transdermal devices.

A further object of the invention is to co-administer estrogens and gestodene transdermally at contraceptively effective rates.

Another object of the invention is to provide a method for the transdermal administration of estrogens and gestodene, in combination.

Yet another object of the invention is to co-administer estrogens and gestodene at contraceptively effective rates from transdermal systems of reasonable size.

These and other objects have been demonstrated by the present invention which provides a method for the transdermal coadministration of a contraceptively effective amount of gestodene and an estrogen, such as ethinyl estradiol, together with a skin permeation-enhancing amount of a suitable permeation enhancer.

The system of the invention is a transdermal drug delivery device comprising a matrix adapted to be placed in drug- and permeation enhancer-transmitting relation with the skin site. The matrix contains sufficient amounts of a permeation enhancer and of an estrogen and gestodene, in combination, to continuously coadminister to the skin for a predetermined period of time the drugs and the permeation enhancer to provide effective contraception. The device is of a reasonable size useful for the application of the drugs and the enhancer to a human body. By "reasonable size", as used herein, is meant a device of a size with a base surface area (that area in contact with the skin site) that is from about 1 cm^2 to about 50 cm^2, preferably from about 5 cm^2 to about 25 cm^2. While devices of as large as 200 cm^2 can be considered to be of "conventional" size, such large sizes are not generally acceptable to women for use for contraception.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a cross-sectional view of one embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with the present invention.

FIG. 2 is a cross-sectional view of another embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with the present invention.

FIG. 3 is a cross-sectional view of yet another embodiment of a transdermal therapeutic drug delivery device which may be used in accordance with this invention.

FIGS. 4a and 4b are graphs showing the in vitro transdermal fluxes of gestodene (FIG. 4a) and ethinyl estradiol (FIG. 4b) from transdermal delivery devices of this invention.

FIG. 5 is a graph showing the comparative in vitro transdermal fluxes of gestodene and levonorgestrel from transdermal delivery devices of 1.6 cm^2 size.

FIG. 6 is a graph showing the in vivo blood plasma levels of gestodene from transdermal delivery devices of 11.4 cm^2 size.

DETAILED DESCRIPTION OF THE INVENTION

This invention utilizes principles of transdermal drug delivery to provide a novel system for effectively administering contraceptives. Particularly, the present invention provides continuous co-administration of an estrogen, such as ethinyl estradiol, and gestodene through the skin or mucosa for up to seven days or longer. A suitable permeation enhancer is present together with the drugs. The flux of the drug formulation provided by this invention is sufficient to achieve contraceptively effective levels of the estrogen and the gestodene from transdermal systems of reasonable size.

One embodiment of a transdermal delivery device of the present invention is illustrated in FIG. 1. In FIG. 1, device 1 is comprised of a gestodene-, estrogen- and permeation enhancer-containing reservoir ("drug reservoir") 2 which is preferably in the form of a matrix containing the drugs and the enhancer dispersed therein. An impermeable backing layer 3 is provided adjacent one surface of drug reservoir 2. Adhesive overlay 4 maintains the device 1 on the skin and may be fabricated together with, or provided separately from, the remaining elements of the device. With certain formulations, the adhesive overlay 4 may be preferable to an in-line contact adhesive, such as adhesive layer 28 as shown in FIG. 3. This is true, for example, where the drug reservoir contains a material (such as, for example, an oily surfactant permeation enhancer) which adversely affects the adhesive properties of the in-line contact adhesive layer 28. Impermeable backing layer 3 is preferably slightly larger than drug reservoir 2, and in this manner prevents the materials in drug

reservoir 2 from adversely interacting with the adhesive in overlay 4. A strippable or removable liner 5 is also provided with device 1 and is removed just prior to application of device 1 to the skin.

FIG. 2 illustrates another embodiment of the invention, device 10, shown in place upon the skin 17. In this embodiment, the transdermal therapeutic delivery device 10 comprises a multilaminate drug formulation/enhancer reservoir 11 having at least two zones 12 and 14. Zone 12 consists of a drug reservoir substantially as described with respect to FIG. 1. Zone 14 comprises a permeation enhancer reservoir which is preferably made from substantially the same matrix as is used to form zone 12. Zone 14 comprises permeation enhancer dispersed throughout and is substantially free of any undissolved estrogen or gestodene. A rate-controlling membrane 13 for controlling the release rate of the enhancer from zone 14 to zone 12 is placed between the two zones. A rate-controlling membrane (not shown) for controlling the release rate of the enhancer from zone 12 to the skin may also optionally be utilized and would be present between the skin 17 and zone 12.

The rate-controlling membrane may be fabricated from permeable, semipermeable or microporous materials which are known in the art to control the rate of agents into and out of delivery devices and having a permeability to the permeation enhancer lower than that of zone 12. Suitable materials include, but are not limited to, polyethylene, polyvinyl acetate and ethylene vinyl acetate copolymers.

An advantage of the device described in FIG. 2 is that the drug-loaded zone 12 is concentrated at the skin surface rather than throughout the entire mass of the reservoir 11. This functions to reduce the amount of drugs in the device while maintaining an adequate permeation enhancer supply.

Superimposed over the drug formulation/enhancer reservoir 11 of device 10 is an impermeable backing 15 and an adhesive overlay 16 as described above with respect to FIG. 1. In addition, a strippable liner (not shown) would preferably be provided on the device prior to use as described with respect to FIG. 1 and removed prior to application of the device 10 to the skin 17.

In the embodiments of FIGS. 1 and 2, the carrier or matrix material has sufficient viscosity to maintain its shape without oozing or flowing. If, however, the matrix or carrier is a low viscosity flowable material, the composition can be fully enclosed in a pouch or pocket formed between the impermeable backing and a permeable or microporous skin-contacting membrane, as known to the art from U.S. Pat. No. 4,379,454 (noted above), for example.

An example of a presently preferred transdermal delivery device is illustrated in FIG. 3. In FIG. 3, transdermal delivery device 20 comprises a drug reservoir 22 containing together the gestodene, the estrogen and the permeation enhancer. Reservoir 22 is preferably in the form of a matrix containing the drugs and the enhancer dispersed therein. Reservoir 22 is sandwiched between a backing layer 24, which is impermeable to both the drugs and the enhancer, and an in-line contact adhesive layer 28. In FIG. 3, the drug reservoir 22 is formed of a material, such as a rubbery polymer, that is sufficiently viscous to maintain its shape. The device 20 adheres to the surface of the skin 17 by means of the contact adhesive layer 28. The adhesive for layer 28 should be chosen so that it is compatible and does not interact with any of the estrogen or gestodene or, in particular, the permeation enhancer. The adhesive layer 28 may optionally contain enhancer and/or drugs. A strippable liner (not shown) is normally provided along the exposed surface of adhesive layer 28 and is removed prior to application of device 20 to the skin 17. In an alternative embodiment, a rate-controlling membrane (not shown) is present and the drug reservoir 22 is sandwiched between backing layer 24 and the rate-controlling membrane, with adhesive layer 28 present on the skin-side of the rate-controlling membrane.

Various materials suited for the fabrication of the various layers of the transdermal devices of FIGS. 1, 2 or 3 are known in the art or are disclosed in the aforementioned transdermal device patents previously incorporated herein by reference.

The matrix making up the gestodene/estrogen/permeation enhancer reservoir can be a gel or a polymer. Suitable materials should be compatible with gestodene, the estrogen, the permeation enhancer and any other components in the system. Suitable matrix materials

include, without limitation, natural and synthetic rubbers or other polymeric material, thickened mineral oil, or petroleum jelly, for example. The matrix is preferably polymeric and is more preferably an anhydrous polymer. A preferred embodiment according to this invention is fabricated from an ethylene vinyl acetate (EVA) copolymer, of the type described in U.S. Pat. No. 4,144,317, and is preferably selected from those EVAs having a vinyl acetate (VA) content in the range of about 9 to 60%, preferably about 28 to 60% VA. Particularly good results may be obtained using EVA of 40% vinyl acetate content.

In addition to gestodene, an estrogen and a permeation enhancer, which are essential to the invention, the matrix may also contain stabilizers, dyes, pigments, inert fillers, tackifiers, excipients and other conventional components of transdermal delivery devices as are known in the art.

The amounts of the estrogen and of gestodene that are present in the therapeutic device, and that are required to achieve a contraceptive effect, depend on many factors, such as the minimum necessary dosage of each drug; the permeability of the matrix, of the adhesive layer and of the rate-controlling membrane, if present; and the period of time for which the device will be fixed to the skin. Since the drugs are to be released over a period of more than one day, there is, in fact, no upper limit to the maximum amounts of the drugs present in the device. The minimum amount of each drug is determined by the requirement that sufficient quantities of drug must be present in the device to maintain the desired rate of release over the given period of application.

The gestodene is generally dispersed through the matrix at a concentration in excess of saturation, i.e. at unit activity. The amount of excess is determined by the intended useful life of the system. However, the drug may be present at initial levels below saturation without departing from this invention. When the estrogen is the natural estrogen 17β-estradiol, it is also generally present in the matrix at a concentration in excess of saturation. However, the concentration of a synthetic estrogen, such as ethinyl estradiol, in the matrix is generally in an amount below saturation, as the flux

of the estrogen through human epidermis has been found to be proportional to the concentration of estrogen in the drug reservoir.

The permeation enhancer is dispersed through the matrix, preferably at a concentration sufficient to provide permeation-enhancing concentrations of enhancer in the reservoir throughout the anticipated administration period.

The permeation enhancer useful in the present invention is selected from those compounds which are compatible with gestodene and with the estrogen and which provide enhanced skin permeation to these two drugs when it is administered together with the drugs to the skin of a user. Additionally, the permeation enhancer must not adversely interact with the adhesive of the in-line contact adhesive layer. Such permeation enhancers can be selected from, but are not limited to, C_{2-4}alcohols such as ethanol and isopropanol, polyethylene glycol monolaurate, dimethyl lauramide, esters of fatty acids having from about 10 to about 20 carbon atoms, and monoglycerides or mixtures of monoglycerides of fatty acids.

Typically, monoglyceride has been available as a mixture of monoglycerides of fatty acids with one monoglyceride being the principal component, from which component the mixture derives its name. For example, one commercial monoglyceride is Emerest] 2421 glycerol monooleate (Emery Division, Quantum Chemical Corp.), which is a mixture of glycerol oleates with a glycerol monooleate content of 58% and a total monoesters content of 58%. Other examples of commercial monoglycerides are Myverol] 1899K glycerol monooleate (Eastman Chemical Products) which has a glycerol monooleate content of 61% and a total monoesters content of 93%, and Myverol] 1892K glycerol monolinoleate which has a glycerol monolinoleate content of 68% and a minimum total monoesters content of 90%. The monoesters are chosen from those with from 10 to 20 carbon atoms. The fatty acids may be saturated or unsaturated and include, for example, lauric acid, myristic acid, stearic acid, oleic acid, linoleic acid and palmitic acid. Monoglyceride permeation enhancers include glycerol monooleate, glycerol monolaurate and glycerol monolinoleate, for example. In a presently preferred embodiment of this invention, the permeation enhancer is a monoglyceride or a mixture of

monoglycerides of unsaturated fatty acids, and more preferred is glycerol monooleate (GMO) or glycerol monolinoleate. As used herein and in the appended claims, the term "monoglyceride" refers to a monoglyceride or a mixture of monoglycerides of fatty acids.

It has been seen that glycerol monooleate having a total monoesters content of less than about 65% interacts adversely with known adhesive materials to such an extent that the adhesive cannot function to maintain a delivery device on the skin. Therefore, when an in-line adhesive is present as a part of the device of the invention so that a permeation enhancer must pass through the adhesive, and when glycerol monooleate is utilized as the permeation enhancer, the glycerol monooleate must have a total monoesters content of at least 65%.

The contraceptive system of the invention contains a drug formulation comprising an estrogen and gestodene.

The term "estrogen" includes both the natural 17β-estradiol and estrone and the semi-synthetic estrogen derivatives such as the esters of natural estrogen, such as estradiol-17β-enanthate, estradiol-17β-valerate, estradiol-3-benzoate, estradiol-17β-undecenoate, estradiol-16,17-hemisuccinate or estradiol-17β-cypionate; 17-alkylated estrogens, such as ethinyl estradiol, ethinyl estradiol-3-isopropylsulphonate, quinestrol, mestranol or methyl estradiol; and non-steroidal compounds having estrogen activity, such as diethylstilbestrol, dienestrol, clomifen, chlorotrianisene or cyclofenil. The drug formulation of the invention preferably contains 17β-estradiol or ethinyl estradiol as the estrogen.

In the present invention, gestodene and an estrogen, such as ethinyl estradiol, are delivered, in combination, at a contraceptively effective rate (that is, a rate that provides effective contraception) and the permeation enhancer is delivered at a permeation-enhancing rate (that is, a rate that provides increased permeability of the application site to both the estrogen and gestodene) for a predetermined time period.

The required transdermal flux for effective contraception as provided by this invention is at least 10 μg/day of ethinyl estradiol or 50 μg/day of 17β-estradiol and at least 50 μg/day of gestodene.

For a 10 cm^2 device, these daily flux values translate to be at least 0.04 $\mu g/cm^2/hr$ for ethinyl estradiol or 0.2 $\mu g/cm^2/hr$ for 17β-estradiol and at least 0.2 $\mu g/cm^2/hr$ for gestodene. For a 3.5 cm^2 device, a flux of at least 0.6 $\mu g/cm^2/hr$ for gestodene is required.

A preferred embodiment of the present invention is a monolith such as that illustrated in FIG. 3 wherein reservoir 22 comprises, by weight, 50-90% polymer (preferably EVA), 0.01-5% estrogen (preferably ethinyl estradiol), 0.1-10% gestodene, and 10-50% permeation enhancer (preferably GMO). The in-line adhesive layer 28 contains an adhesive which is compatible with the permeation enhancer. In the presently preferred embodiment, there is no rate-controlling membrane.

The devices of this invention can be designed to effectively deliver an estrogen and gestodene for an extended time period of up to 7 days or longer. Seven days is generally the maximum time limit for application of a single device because the skin site is adversely affected by a period of occlusion greater than 7 days. The drug delivery must be continuous in order to provide effective contraception. Therefore, when one device has been in place on the skin for its effective time period, it is replaced with a fresh device, preferably on a different skin site. For example, for a 7-day device, maintenance would involve replacing the device every 7 days with a fresh device and continuing said replacement for as long as contraception was desired. In an alternative method of obtaining effective contraception, it may be desired to apply devices containing gestodene and estrogen for a period of 3 weeks, followed by application for 1 week of a device as disclosed herein but containing only the estrogen.

The transdermal therapeutic devices of the present invention are prepared in a manner known in the art, such as by those procedures, for example, described in the transdermal device patents listed previously herein.

The following examples are offered to illustrate the practice of the present invention and are not intended to limit the invention in any manner.

The devices for Examples 1 and 2 are prepared as follows:

A. Control Formulation (No Permeation Enhancer)

A control formulation containing 6% gestodene in a matrix of EVA 40% VA ("EVA 40") was prepared by dissolving gestodene and EVA 40 in methylene chloride. The solution was poured onto an FCD/polyester release liner to evaporate. The dried material was then pressed to 4-5 mil (ca. 0.1 mm) thickness between two sheets of FCD/polyester release liner at 75°C. The resulting film was heat-laminated to an impermeable backing (Medpar® or Scotchpak®, for example), and 1.6 cm^2 discs were punched or die-cut from the laminate.

B. Formulations Containing Permeation Enhancers

Formulations containing various gestodene concentrations (0%, 2%, 4%, 6% and 8%), various permeation enhancers, and various permeation enhancer concentrations (0%, 25%, 30% and 35%) in a matrix of EVA 40 were prepared by dissolving the necessary components in methylene chloride and following the same procedures as for the control formulation.

"M-GMO" is Myverol® 1899K monoglyceride mixture (Eastman Chemical Products), having a glycerol monooleate content of 61% and a total monoesters content of 93%. Myverol® 1892K monoglyceride mixture (Eastman Chemical Products) has a glycerol monolinoleate content of 68% and a total monoesters content of 90%. "GML" is glycerol monolaurate (Grindtek] ML 90, Grindsted Products A/S).

C. Devices with In-line Adhesive

Each of the drug matrix/impermeable backing laminates were divided in half, and one-half of each were laminated to 3M acrylate transfer adhesive MSP 32589 (1.6 mil; an acrylate adhesive with 2-5% acid functionality). Before testing, each final laminate was equilibrated for at least 5 days to allow the enhancer and the drugs to partition into the contact adhesive. The edges of the devices with in-line adhesive were masked with polyester tape so that the drug reservoir edges were not exposed to the epidermis or solutions when they were tested.

EXAMPLE 1

The in vitro transdermal gestodene fluxes with Myverol 1899K (M-GMO), Myverol 1892K, and GML were compared against a no-enhancer control, with and without an in-line adhesive, on epidermis from one human donor.

The epidermis was separated from the dermis of the skin donor after immersion in 60°C water for 75 seconds. Discs (7/8-inch diameter) were cut from the epidermis, and the discs were kept at 4°C in a hydrated state until they were used.

For each device tested, the release liner was removed and the drug-releasing surface was placed against the stratum corneum side of a disc of epidermis which had been blotted dry just prior to use. The excess epidermis was wrapped around the device so that none of the device edge was exposed to the receptor solution. The device covered with epidermis was attached to the flat side of the Teflon holder of a release rate rod using nylon netting and nickel wire. The rods were reciprocated in a fixed volume of receptor solution (distilled water). The entire receptor solution was changed at each sampling time. The temperature of the receptor solution in the water bath was maintained at 35°C.

A summary of the results is given in Table I below.

TABLE I

Gestodene Transdermal Flux

Skin Donor A
Average Transdermal Gestodene Flux, 7-96 hours, $\mu g/cm^2hr$

wt% Permeation Enhancer	30	30	30	30	35	0
wt% Gestodene	2.0	4.0	6.0	8.0	4.0	6.0
Permeation Enhancer						
Myverol 1892 K						
Without Adhesive	--	0.37	--	0.43	--	0.08
With Adhesive	--	0.44	--	0.39	0.42	--
Myverol 1899 K (M-GMO)						
Without Adhesive	0.88	0.57	--	--	--	
With Adhesive	0.50	0.37	0.43	0.46	--	
GML						
Without Adhesive	--	0.34	--	0.47	--	
With Adhesive	--	0.34	--	0.26	0.37	

EXAMPLE 2

The in vitro transdermal gestodene fluxes of M-GMO- and GML-containing formulations were compared against a no-enhancer control, with and without an in-line adhesive, on the epidermis from three human donors, following the procedures of Example 1. A summary of the results is given in Table II below.

TABLE II

Gestodene Transdermal Flux

Skin Donors A, B, and C; n=3 each unless otherwise noted
Average Transdermal Gestodene Flux, 7-96 hours, μg/cm²hr

Permeation Enhancer	None	M-GMO	M-GMO	GML	GML
wt% Permeation Enhancer	0	30	30	35	35
wt% Gestodene	6.0	4.0	4.0	4.0	4.0
Adhesive	None	None	MSP 32589	None	MSP 32589
				n=2 each	
Skin Donor A	0.11 ± 0.02	1.23 ± 0.32	0.73 ± 0.20	0.65	0.48 ± 0.09
Skin Donor B	0.16 ± 0.05	2.42 ± 0.80	1.27 ± 0.39	0.91	0.37 ± 0.09
Skin Donor C	0.19 ± 0.03	3.63 ± 1.16	1.57 ± 0.66	0.99	0.56 ± 0.06
Average Donors A, B, and C	0.15 ± 0.05	2.45 ± 1.27	1.19 ± 0.54	0.85 ± 0.26	0.47 ± 0.11

The MSP 32589 contact adhesive is compatible with the Myverol GMO permeation enhancer; that is, the enhancer does not destroy the adhesive characteristics of the adhesive material.

It has now been found that in addition to its adhesive function, the MSP 32589 contact adhesive also functions to control to some degree the release rate of gestodene and ethinyl estradiol from the drug reservoir. However, the amount of gestodene and estradiol that is administered through the adhesive layer to the surface of the skin is still in excess of that which the area of skin is able to absorb. Additionally, and more importantly, the MSP 32589 adhesive appears to effectively control the rate of absorption of gestodene and of estradiol into the skin by controlling the release rate of the M-GMO permeation enhancer from the reservoir. The release rate of the M-GMO is below the maximum rate the area of skin is able to

absorb and is sufficient to increase the permeability of the area of skin to the gestodene and estradiol such that the drugs are absorbed at a rate that provides a therapeutically effective level of the drugs in the bloodstream of the patient. These functions are illustrated in the following Example 3.

EXAMPLE 3

The in vitro release rates and transdermal fluxes of gestodene from transdermal devices similar to those of Examples 1 and 2 (containing 6% gestodene in an EVA 40 matrix) were tested. The devices were either with or without M-GMO permeation enhancer and with or without MSP 32589 in-line adhesive. The results are presented in Table III below, and indicate that the release of gestodene from the devices was somewhat less when the adhesive was present. In both cases, while sufficient gestodene was released, it had no appreciable flux through skin unless M-GMO was present. Additionally, the results show that the transdermal flux of gestodene in the presence of M-GMO was significantly less (although still sufficient to provide a contraceptive effect) when the adhesive was present than when it was absent.

TABLE III

		Gestodene ($\mu g/cm^2$, 0-72 hr)	
Myverol 1899K (M-GMO)	MSP 32589 Adhesive	Release Rate	Transdermal Flux
0%	-	570	6
30%	-	450	70
0%	+	320	4
30%	+	590	32

EXAMPLE 4

A transdermal therapeutic device as described with respect to FIG. 3 for the administration of ethinyl estradiol and gestodene was formulated from: 3.0 wt% (weight percent) gestodene, 0.3 wt% ethinyl

estradiol, 66.7 wt% EVA 40, and 30.0 wt% M-GMO. In-line adhesive MSP1006P (same as MSP32589 but of 2.0 mil thickness; 3M) was also present. The in vitro skin flux was measured, following the procedures of Example 1, and is presented in FIG. 4a (flux of gestodene) and FIG. 4b (flux of ethinyl estradiol). The results presented in FIGS. 4a and 4b are the average ± one standard deviation.

EXAMPLE 5

The in vitro transdermal flux of gestodene was compared with that of levonorgestrel as follows.

Gestodene-containing transdermal devices were prepared comprising gestodene, in an amount greater than saturation, and 30 wt% Myverol 1899K in an EVA 40 matrix and with an in-line MSP 32589 adhesive layer. Levonorgestrel-containing transdermal devices were prepared comprising levonorgestrel, in an amount greater than saturation, and 25 wt% Myverol 18-99K in an EVA 40 matrix and with an in-line adhesive layer of MSP 121388 acrylate adhesive (with 2-5% acid functionality; 3M). Each device was 1.6 cm^2 in size. Three of each of the gestodene- and the levonorgestrel-containing devices were placed on the skin of each of three human cadaver donors. The flux of each of the two drugs through the epidermis was determined at various time points, following the procedures of Example 1. The results, shown in FIG. 5, indicate that levonorgestrel ("LNG") has a very low flux through human cadaver epidermis with this reasonably sized system, while that of gestodene is substantially greater.

EXAMPLE 6

The in vivo blood plasma levels of gestodene over 96 hours was determined as follows.

Gestodene-containing transdermal devices of 11.4 cm^2 size were prepared comprising 4.0 wt% gestodene and 30 wt% Myverol 1899K in an EVA 40 matrix and with an in-line MSP 32589 adhesive layer. One device was placed on each of two human volunteers and blood samples were taken at intervals over 96 hours for determination of the level of gestodene present in the blood plasma. The results are presented

in FIG. 6. After about 30 hours, subject 1 reported that the adhesion of the device was not good. This problem persisted for the remainder of the test period, and the plasma levels of gestodene in this subject declined as a result. The device originally placed on subject 2 was lost during the first night; another device was applied at 24 hours. After rising to a steady state, the amount of gestodene in the plasma of subject 2 was maintained at this high level until the device was removed.

This invention has been described in detail with particular reference to certain preferred embodiments thereof, but it will be understood that variations and modifications can be effected within the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A composition of matter for the transdermal administration of a drug formulation comprised of an estrogen and gestodene, the composition comprising, in combination, a contraceptively effective amount of the drug formulation and a skin permeation-enhancing amount of a suitable permeation enhancer.

2. A method for the transdermal administration of a drug formulation comprised of an estrogen and gestodene, which method comprises:

(a) administering the drug formulation at a contraceptively effective rate to an area of skin, the area being from about 1 cm^2 to about 40 cm^2 in size; and

(b) simultaneously administering a suitable permeation enhancer to the area of skin at rates which are sufficient to substantially increase the permeability of the area to the drug formulation.

3. A method for providing contraception to a woman, which method comprises:

(a) administering a drug formulation comprised of an estrogen and gestodene at a contraceptively effective rate to an area of the woman's skin, the area being from about 1 cm^2 to about 50 cm^2 in size; and

(b) simultaneously administering a suitable permeation enhancer to the area of skin at rates which are sufficient to substantially increase the permeability of the area to the drug formulation.

4. A device for the transdermal administration, at a contraceptively effective rate, of a drug formulation comprised of an estrogen and gestodene, which device is of a reasonable size and comprises:

(a) a reservoir comprising a matrix containing a contraceptively effective amount of the drug formulation

and a skin permeation-enhancing amount of a suitable permeation enhancer;

(b) an impermeable backing on the skin-distal surface of the reservoir; and

(c) means for maintaining the reservoir in estrogen-, gestodene- and permeation enhancer-transmitting relation with the skin.

5. A device for providing contraception to a woman, which device is of a reasonable size and comprises:

(a) a reservoir comprising a matrix containing a contraceptively effective amount of a drug formulation, the drug formulation comprised of an estrogen and gestodene, and a skin permeation-enhancing amount of a suitable permeation enhancer;

(b) an impermeable backing on the skin-distal surface of the reservoir; and

(c) means for maintaining the reservoir in estrogen-, gestodene- and permeation enhancer-transmitting relation with the skin.

6. A composition, method or device according to claim 1, 2, 3, 4 or 5 wherein the estrogen is ethinyl estradiol.

7. A composition, method or device according to claim 1, 2, 3, 4 or 5 wherein the permeation enhancer is a monoglyceride.

8. A composition, method or device according to claim 1, 2, 3, 4 or 5 wherein the permeation enhancer is glycerol monooleate, glycerol monolinoleate, or glycerol monolaurate.

9. A composition, method or device according to claim 1, 2, 3, 4 or 5 wherein the estrogen is ethinyl estradiol and the permeation enhancer is glycerol monooleate.

10. A method or device according to claim 2, 3, 4 or 5 wherein the estrogen is ethinyl estradiol and the ethinyl estradiol is administered through the skin at a rate of at least 10 μg/day for a predetermined period of time, and the gestodene is administered through the skin at a rate of at least 50 μg/day for a predetermined period of time.

11. A device according to claim 4 or 5 wherein the estrogen is ethinyl estradiol, the permeation enhancer is glycerol monooleate and the matrix comprises ethylene vinyl acetate copolymer having from about 9 to 60% vinyl acetate.

12. A device according to claim 11 wherein the means for maintaining the reservoir in relation with the skin comprises an in-line adhesive layer on the skin-proximal surface of the reservoir and the glycerol monooleate has a total monoesters content of at least 65%.

FIG. 1

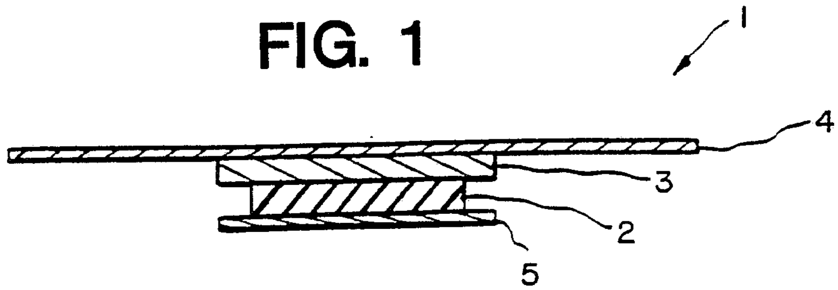


FIG. 2

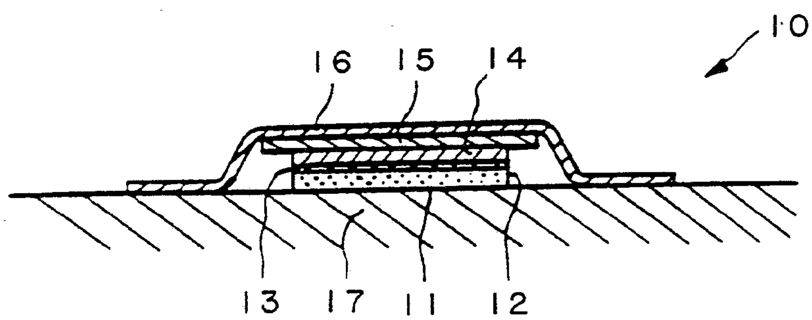


FIG. 3

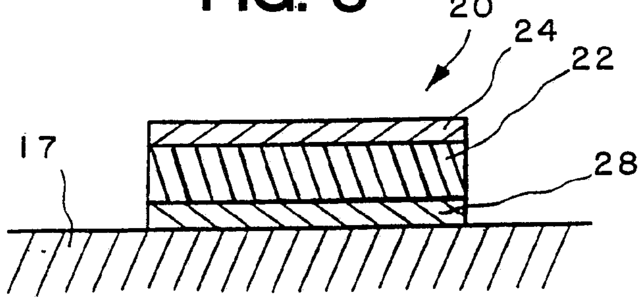


FIG. 4A

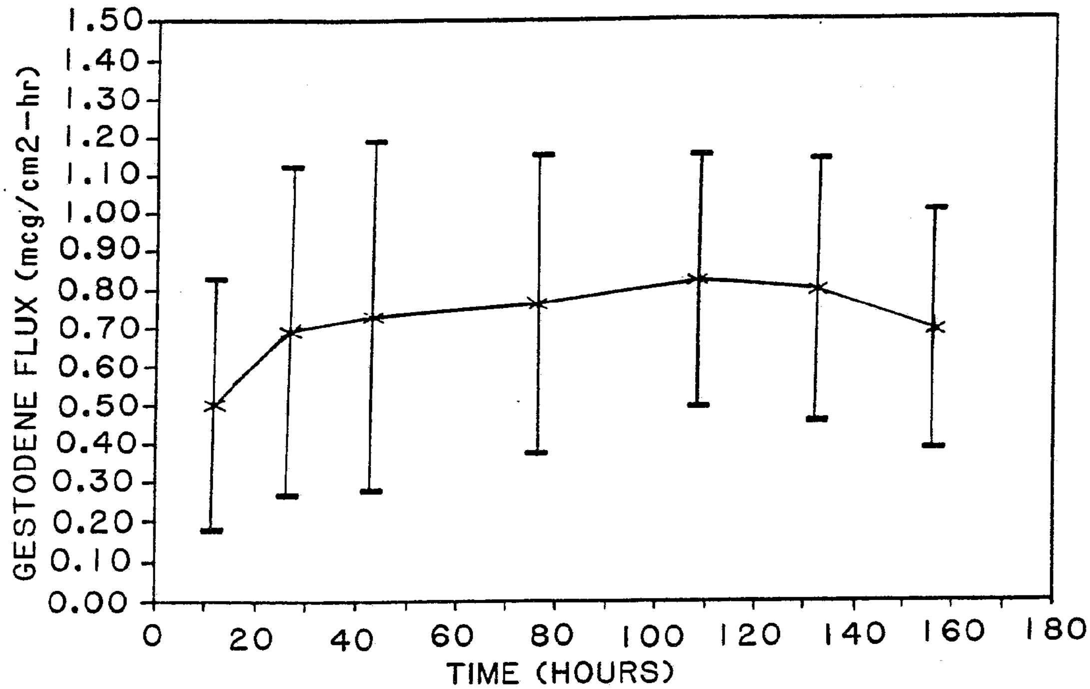

GESTODENE FLUX (mcg/cm2-hr)
1.50
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0
20
40
60
80
100
120
140
160
180
TIME (HOURS)

FIG. 4B

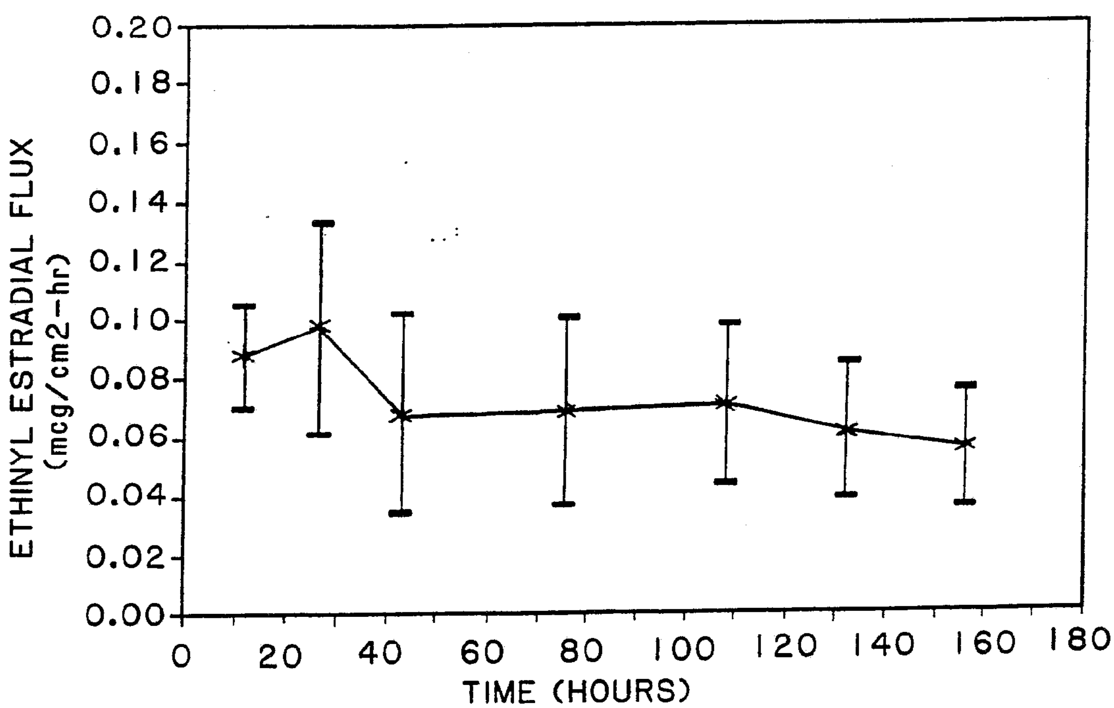
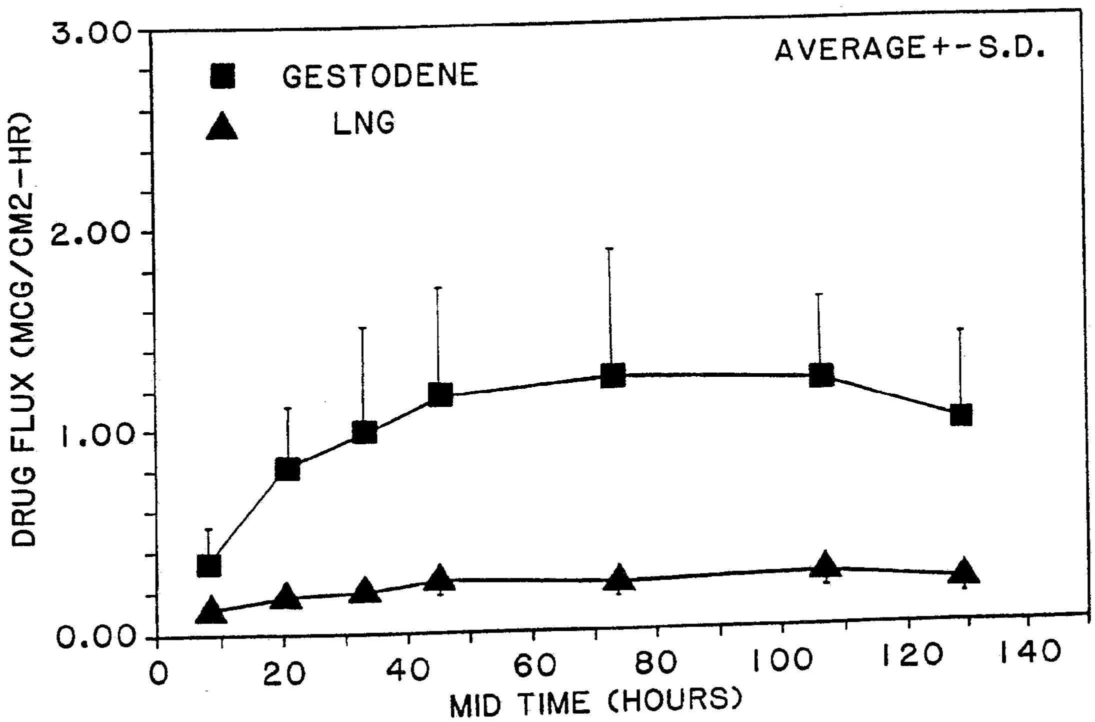
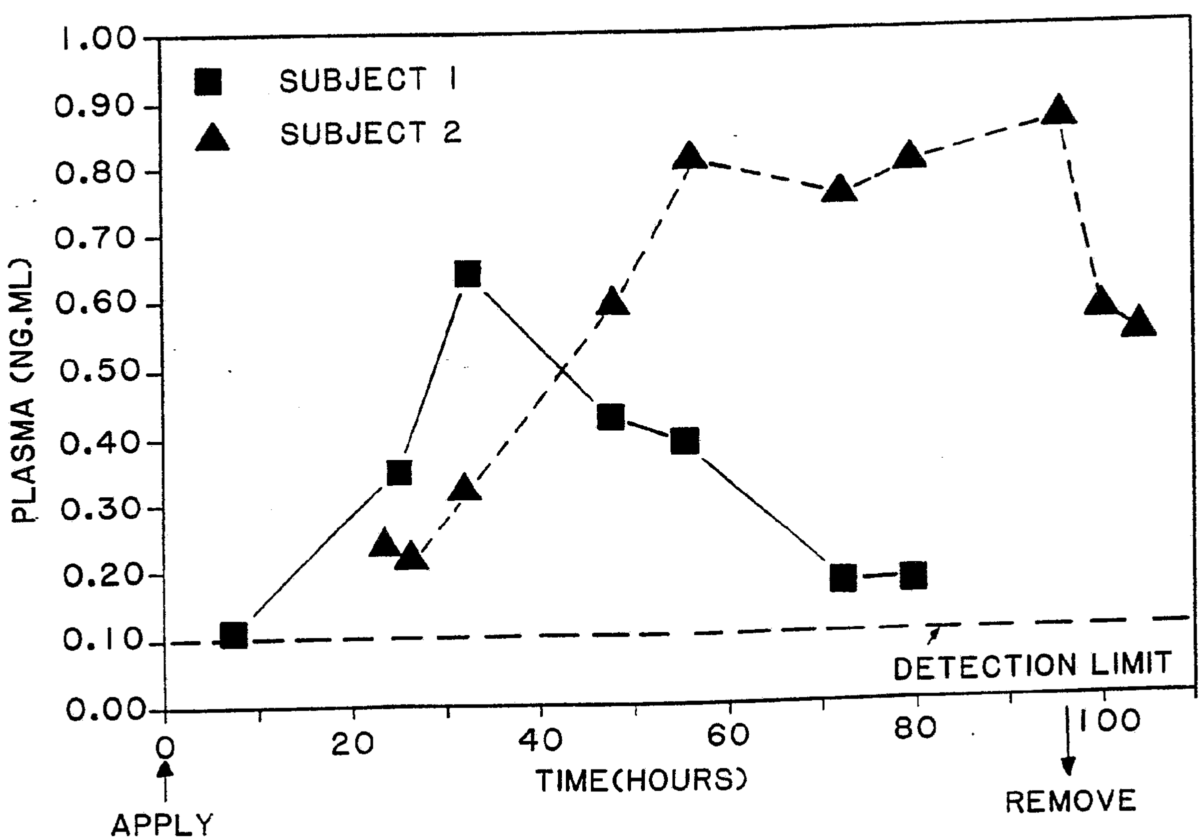

ETHINYL ESTRADIAL FLUX (mcg/cm2-hr)
0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
20
40
60
80
100
120
140
160
180
TIME (HOURS)

FIG. 5



AVERAGE+-S.D.
GESTODENE
LNG
DRUG FLUX (MCG/CM2-HR)
3.00
2.00
1.00
0.00
0
20
40
60
80
100
120
140
MID TIME (HOURS)

FIG. 6



SUBJECT 1
SUBJECT 2
PLASMA (NG.ML)
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
DETECTION LIMIT
0
20
40
60
80
100
TIME(HOURS)
APPLY
REMOVE

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/07984

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 L 15/16 A 61 K 31/565 A 61 K 47/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 L A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X Y	EP,A,0370220 (SCHERING AG) 30 May 1990, see page 2, lines 1-23; page 2, line 51 - page 3, line 15; page 3, line 52 - page 4, line 12; page 4, line 22-36; page 4, lines 52-55; page 4, example 3; claims ---	1-6 7-12
Y	EP,A,0279982 (ALZA CORP.) 31 August 1988, see page 3, lines 3-7; page 4, example 1; claims -----	7-12

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-02-1992	27 FEB 1992
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	MISS T. TAZELAAR

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9107984 SA 53817

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 18/02/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0370220	30-05-90	DE-A- 3836862	03-05-90
		DE-A- 3910578	04-10-90
		AU-A- 4374789	03-05-90
		CA-A- 2001618	27-04-90
		WO-A- 9004397	03-05-90
		EP-A- 0394429	31-10-90
		JP-T- 3502700	20-06-91
EP-A- 0279982	31-08-88	US-A- 4816258	28-03-89
		AU-B- 594908	15-03-90
		AU-A- 8298287	01-09-88
		JP-A- 63225319	20-09-88
		ZA-A- 8708499	10-05-88

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82